INTERNATIONAL CORNER

ORAL CONTRACEPTION IN THE NEW MILLENIUM

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INTRODUCTION

Hormonal contraception was introduced for preventing pregnancy in 1960 and actually 78 million women world-wide use it (1).
Oral contraceptives (OCs) are the most reversible effective contraceptive method, under conditions of perfect use the rate of failure is 0.1%, but with inattentive use (missed pills, starting the active pill cycle early or late, sporadic use, or discontinuation) the failure rate rises up to 5% (2).
A wide range of non contraceptive health benefits have subsequently been attributed to their use: treatment of dysfunctional bleeding, preservation of bone density, reductions in dysmenorrhea, in anemia, in risk of ectopic pregnancy and in fibrocystic breast change.
Many studies were performed to investigate about the safety of oral contraceptives (OCs). Subsequently, cardiovascular risks and neoplastic effects nearly overshadowed the numerous benefits offered by the use of OCs.

CARDIOVASCULAR EFFECTS

When oral contraceptives were first introduced, the high doses of estrogens they contained were associated with an increased risk of cardiovascular events. In the following four decades, the estrogen dose in OCs have been reduced steadily, so that current low estrogen-dose (<35 mcg) are associated with a lower risk of cardiovascular events. Unfortunately, the data from the early epidemiological studies are still reflected in the product labelling for all the currently used OC and continue to affect women's perceptions regarding OC safety.
It is also important to define the cardiovascular events associated with OC use according to whether they involve the venous or the arterial districts; the main venous events is venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. On the other hand the main arterial events are ischemic or hemorrhagic stroke and myocardial infarction.
Thus, the vascular effects observed on both the venous and arterial district are the results of unfavourable metabolic and thrombophilic effects (3). A major metabolic consequence of the estrogen in OC formulation is to increase the synthesis of hepatic globulins. The increased synthesis of angiotensinogen, that is converted in angiotensin, results in an increase of blood pressure (4); other globulins are involved in enhancing thrombophilia.

Oral Contraceptives And Venous Thromboembolism

Intravascular clotting is normally prevented by the continuous regulation of procoagulatory factors, coagulation inhibitors and the fibrinolitic system in the vessel wall.

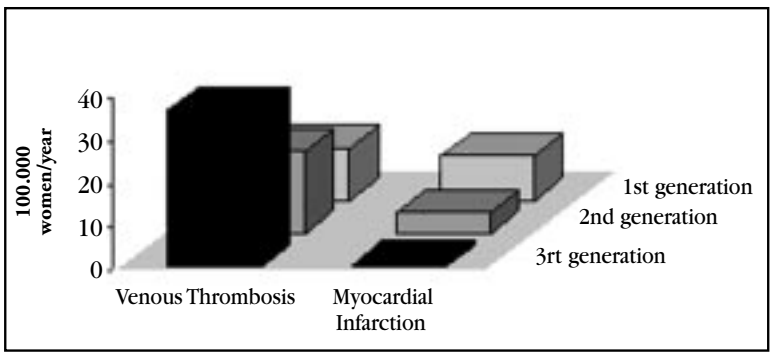
In the general population the incidence of venous thromboembolism is 2-6 events per 100.00 women/year, this individual risk is influenced by thrombophilic conditions: genetic mutations or secondary hypercoagulable state resulting from various diseases (malignancy, recent surgery, obesity), pathophysiological states (pregnancy, immobilization) or drug administration.
Combined OC have long been known to have an effect on hemostatic parameters, an increase in fibrinogen, fibrinopeptide A, coagulation factors (V, VII, VIII, X), prothrombin fragment 1-2 and thrombin-antithrombin complexes have been described in OC user (5, 6). Also fibrin degradations products and D-dimer levels are increased (7).
The early reports appearing in the mid to late 1960s described a several-fold times higher risk of thromboembolic events among OC users than among non-users, a finding that was subsequently found to be dose-related because of all the effects on coagulation are strictly related to the dose of ethynyl-estradiol (EE) present in the OC formulation.
It was found that the rate of venous thromboembolism (VTE) among women using OC formulations containing > 50 mcg EE was 100 per 100.000 woman-years, which was higher than the rate of 70 per 100.000 woman-years found in users of 50 mcg EE- OC, more than twice as great as the rate of 42 per 100.000 woman-years in users of OC containing < 50 mcg EE (8).
Subsequent epidemiological investigations have continued to demonstrate that, even with low-dose OC containing ≤ 35 mcg estrogen, the risk of VTE is increased three to four fold compared with non-users. A five-year case control study demonstrates that, after adjusting for progestin type and length, with 30-40 mcg EE OCs as reference, 20 mcg EE products implied odd ratios (ORs) of 0.6 (0.4-0.9) and 50 mcg EE products implied ORs of 1.6 (0.9-2.8) (9). In fact the changes in coagulation factors, fibrinopetide A and fibrinogen are more pronounced with high dose preparations, and are frequently less affected or absent in users of pills containing ≤ 30 mcg EE (10).
Several epidemiological studies published in 1995 and 1996 (11,12), not confirmed by others (13-16), reported a difference between the risk of VTE in women using third-generation OCs containing desogestrel (GSD) or gestodene (GSD), and those using second-generation OCs containing the some dose of EE but combined with one of the older progestogens, levonorgestrel (LNG) or norgestimate (NGM).
A recent meta-analysis, after stratifying by various factors and examining selected subgroups shows that third generation OCs are associated with a 1.7-fold increased risk of VTE compared with second generation OCs (17). In clinical terms the baseline incidence in women using second-generation OCs would be doubled in women taking third generation

OCs. The incidence would increase from approximately 19 to 36 per 100.000 woman/years, with an absolute excess risk, in terms of increased incidence, of 17 per 100.000 woman/years (18).
A recent review analysing 17 comparative studies on the hemostatic effects of DSG/GSD and LNG/NGM containing OCs, found no consistent, significant differences or trends suggesting increased thrombogenicity of third generation progestogens, except for increased FVII activity (19). The difference in FVII activity between OCs may, therefore, reflect differences in lipid/lipoprotein metabolism between their progestogen components.
It is important to consider that the relative risk of fatal pulmonary embolism in current users of OCs is estimated of 9.6 (3.1-29.1) with an absolute risk of death from pulmonary embolism of 10.5 per million woman-years (20).
It seems safe to conclude that any potential differences in cardiovascular risk that may exist are of little relevance with their public health impact (16).

Oral Contraceptives And Myocardial Infarction

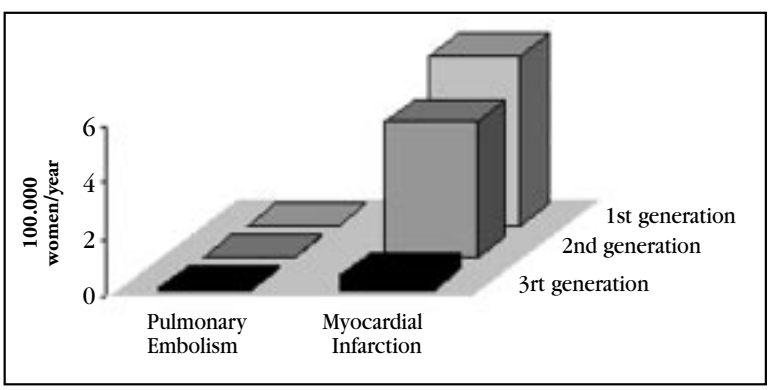
The first report of coronary thrombosis associated with the use of OCs appeared in 1963 (21), subsequently the association between OC use and acute myocardial infarction was established in studies which took place during 1960 and 1970. The preparations assessed in these studies contained ≥ 50 mcg of EE, the relative risk estimates ranged from about 2 to 5 for the overall comparison of current OC users to non-users (23).
Several observational studies have shown that the most independent risk factor for MI among OC users is cigarette smoke, the combination of OC use and smoking is synergistic, increasing the relative risk by as much as 30 fold (23).
The incidence of myocardial infarction (MI) is age-related, it's a rare diagnosis in women aged less than 45 and deaths caused by MI among non-smoking women are even more rare (18).
Moreover, the relative risk of MI is almost 4-fold higher among current OC users with a history of hypertension than in normotensive women (24). The combination of these risk factors is synergistic, in fact according to WHO a history of severe hypertension in current OC users increased the relative risk as 17-fold (25).
The estrogens and progestins contained in OC have variable metabolic effects, all of which can ultimately affect the arterial side of the cardiovascular system. Both hormonal components can produce insulin resistance, but this effect was much more marked in high-estrogen dose OC or in OC containing early progestins.
Estrogen has a favourable effect on serum lipids and lipoproteins, producing an increase in HDL, as well as a decrease in LDL and total cholesterol. The early hormonal combinations contain estrane progestins or levonorgestrel which tended to oppose the positive effect of estrogen on HDL/LDL cholesterol ratio. The development of more selective gonane progestins (gestodene, desosogestrel), as well as drospirenone, all led to a favourable effect on the HDL/LDL ratio (26). It has been suggested that the favourable effect on the lipid profile by using third generation contraceptives can protect against cardiovascular disease such as myocardial infarction.
In 1998 the Danish study demonstrate a reduction of relative risk for MI in women who used third generation OC (RR=0.8: 0.15-1.7) compared to women who used second generation OC (RR=1.9: 0.7-4.9) (27).
The Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study is a nationwide, population-based, case control study of the relation of the use of OC among women 18 to 49 years; were enrolled 248 women who had had a first myocardial infarction between 1990 and 1995 and 925 control women matched for age and area of residence. The results of the RATIO study confirm that women using any type of OC as compared with non-users had a odds ratio for MI of 2.0 (1.5-2.8), but there are differences according to the type of progestins. The adjusted odds ratio was 2.% (1.5-4.1) among women who used second generation OC and 1.3 (0.7-2.5) among those who used third generation OC (28).
Although the risk of myocardial infarction in users of OC is small in absolute terms, according to WHO recommendations the use of OC in non-smoking, normotensive, non-diabetic women is absolutely safe in young women (aged < 35 years). OCs containing 35 mcg or less of estrogen can be used in 35 years or younger women who smoke, however the use of OCs is contraindicated in women 35 years who smoke (19). The results with respect to the use of third generation OC were inconclusive but suggested that the risk was lower than the risk of MI associated with second generation OC (28).
A comparison between the absolute incidence of cardiovascular disease in women using different OCs formulations show that third generation OCs has a two-fold increase of incidence of VTE compared to second generation OCs. Instead the absolute incidence of MI is lower in women who use third generation OCs than incidence associated with second generation OCs (Fig.1).

Figure 1: Incidence of cardiovascular disease in women using OC



Considering fatal cardiovascular events the relative risk of fatal pulmonary embolism in women using OCs is very low, in clinical terms the number of annual events of pulmonary embolisms in OCs containing gestodene or desogestrel is lower than the absolute incidence of myocardial infarction (Fig. 2). From these data it does not appear appropriate

Figure 2: Incidence of cardiovascular disease in women using OC



to prescribe third generation OCs, in order to reduce the cardiovascular impact of these compounds.

Oral Contraceptives And Ischemic Stroke

Stroke is a rare event in young women (aged < 45 years) and follows an age-related pattern. In common with myocardial infarction there are several risk factors for ischemic stroke including history of hypertension and smoking. In women with hypertension, the RR of ischemic stroke increases almost 4-fold, among smokers the increase is slightly more than 3-fold (26). In addition, a history of migraine, in particular with aura, is an important risk factor for ischemic stroke (RR =6) and highly increase the RR of stroke in OCs users (RR=14).
The association between use of OCs and ischemic stroke was established in 1960. Since then, many study demonstrate an increased risk of cardiovascular diseases in OC users, however it's important to consider the estrogen dose and the type of progestins contained in OC.
A meta-analysis reviewed the medical literature published since 1960 to 1999 and included the RR estimation of 16 independent studies and all these 16 studies showed a positive association between current OC use and ischemic stroke risk. The overall summary risk estimate for ischemic stroke in current OC users compared with those not currently use OCs was 2.75 (2.24-3.38). The risk was less with lower estrogen dosages, falling form a RR of 4.53 (2.17-9.50) with more than 50 mcg to a RR of 2.08 (1.55-2.80) with less than 50 mcg. Analysis of progestins type suggested non significant decreasing risk with the newer formulations, with a RR of 3.05 (2.37-3.92) in second-generation preparation and a RR of 2.11 (0.96-4.64) in third-generation preparations (29).
The RATIO study reports that the risk of stroke in women using any type of OCs versus none was 2.3 (1.6-3.3). Use of OCs with EE doses ≥ 50 mcg (irrespective to the progestogen content) versus no use was associated with an OR for stroke of 3.1 (1.2-7.9), this was higher than OR of preparations with < 50 mcg EE (2.3: 1.5-3.4). Compared with nonusers, the OR for stroke in women who used second-generation OCs was 2.4 (1.6-3.7) and for women on third-generation OCs it was 2.0 (1.2-3.5). Third generation OCs confer the same risk of ischemic stroke as second-generation OCs and the risk did not change after additional adjustment for putative confounding factors (30).
With a RR of 1.93 due to low-estrogen OCs, a woman's annual stroke risk would be expected to increase from 4.4 to 8.5 per 100.000 based on background incidence rates (31). Therefore, treatment of 24.000 women would be expected to lead to a single additional ischemic stroke each year (29).

ORAL CONTRACEPTIVES AND NEOPLASIA

The evaluation of the different neoplastic effects associated with the OCs use is the aim of several studies since the introduction of hormonal contraception.
An important point of discussion is about an increase in breast cancer risk among women who were current users of an OC, or had recently stopped using an OC. Most studies have confirmed that OCs moderately increase the risk of cervical cancer, particularly in human papilloma virus (HPV)-positive women.
On the contrary, recent epidemiological studies have confirmed that combined OCs provide substantial protection against endometrial and ovarian cancers, and results suggest that such protection is long-lasting, and may persist for 15 years or more after stopping OC use (32).
Several studies have suggested an inverse relationship between use of OCs and risk of colorectal cancer, and in a meta-analysis of published data the pooled relative risk of colorectal cancer for DC ever-use was 0.82 (95% confidence interval 0.74 to 0.97) (33). There was no association with duration of use. The increased risk for hepatocellular carcinoma in the absence of hepatitis B viruses is the only established evidence of a direct association between OC use and cancer risk, which led an International Agency for Research on Cancer Working Group to classify OCs as carcinogenic to humans in 1998 (33).
No association was observed between combined OC use and the incidence of skin melanoma, or any other common skin neoplasm. In terms of clinical and public health implications, the most relevant points regarding OC use are: recent data confirm that OCs confer persistent protection against ovarian cancer and any increased risk of breast cancer in OC users is moderate and is restricted to current/recent users. This is reassuring for younger women, whose baseline risk of this disease is extremely low (32).

Breast Cancer And Oral Contraceptives

The possibility of a link between OC use and breast cancer has led to intensive research, but past studies have provided inconstant results, causing controversy among investigators and anxiety among clinicians and patients. The clinical and the epidemiological evaluations indicate that breast cancer is hormonally mediated, although biologic mechanisms are not established both components of combined OCs, estrogen and progestins, have been implicated in tumor initiation and promotion (34).
An extensive re-analysis made by the Collaborative Group on Hormonal Factors in Breast Cancer in 1992 answered some very significant questions about OC use and breast cancer risk. It was clearly demonstrated that the estrogen dose, progestin type and duration of use do not increase the risk of diagnosis of breast cancer. In addition the re-analysis showed that hormonal contraception use does not increase breast cancer risk in women who use OCs at a very young age or before their first childbirth or who have family history of breast cancer. However, among the women currently using OCs, and during the 10 years after discontinuation of OC use, there is a small increase of breast cancer diagnosis. The RR of breast cancer diagnosis in current users is 1.24 (1.15-1.33); 5 to 9 years after stopping OC the RR is 1.07 (1.02-1.13). Ten years after discontinuation of OC use there is no evidence of an increased risk of diagnosis of breast cancer compared with never-users.
It's important to report that the diagnosis of breast cancer was limited to localized disease and there was a reduction of tumors that had spread beyond the breast. These findings may reflect increased monitoring of OCs users or may suggest that OCs stimulate growth of a previously non-evident breast, thus enabling early diagnosis (35, 36).
To determine how many of the additional cases of breast cancer found in OC users are attributable to OC use, Collins conducted a meta-analysis of 10 studies performed in women with breast cancer. The obtained estimates of the relative risk of breast cancer among OC users were compared with no users according to age at time of diagnosis. The results were applied to reported annual incidence rate of breast cancer. In a theoretical population of 10.000 OC users and 10.000 non users, there would be 17 diagnosis of breast cancer in non users younger than age 35 and 26 diagnosis in OC users the same age, for a total of 9 additional cases among OC users. In women aged 35 to 54 OC users 12 cases fewer than non users would be expected. Accordingly, a net reduction of 3 cases would be expected among OC users when considering all women up to 55 years of age (37).
The Collaborative Group estimated that for women in Europe or North

America, 5 years of OC use was associated with an excess of 0.05 to 3.2 of breast cancer per 1000 women, depending on age at use (35, 36).
The causal association between OCs use and breast cancer is not fully understood. Estrogen is a known mitogen to breast epithelial cells, but there is still a controversy about the effect of added progestogens.
During a study 26 women biopsies were performed before and after 2 months of OC use, there was a positive correlation between proliferation and progesterone levels in non-users and with serum levonorgestrel concentrations in women using OCs containing this progestogen (rs = 0.43, p = 0.02). Women using OCs had significantly lower serum androgen levels compared to naturally cycling women and free testosterone levels displayed an inverse relation to breast epithelial proliferation (38). The results add to the growing evidence that progestogens may be mitogenic in breast tissue. Increased proliferation during hormonal contraception should be regarded as an unwanted and potentially hazardous side effect. Efforts should be made to define hormonal contraceptive regimens which minimize breast epithelial proliferation and to identify those women with the most pronounced proliferative response.

Ovarian Cancer And Oral Contraceptives

An indication of the long-term favourable impact of OCs on ovarian carcinogenesis comes from descriptive epidemiology. In several developed countries, in fact, young women showed substantial declines in ovarian cancer incidence and mortality. Cohort analysis of trends in mortality from ovarian cancer indicated that women born after 1920, from the generation of mothers who had use OCs, showed consistently lower ovarian cancer rates, and the downward trends were greatest in countries where OCs were more widely utilized (39).
Quantification of the real long-term effect of OCs on ovarian carcinogenesis, remains, however, open to discussion. With short term OC use, the reduction in risk for epithelial ovarian cancer is about 40% and with long term use (>10 year) the reduction in risk is 80% (40). These risk reductions are independent from histological types of epithelial ovarian cancer.
The favourable effect of OCs on epithelial ovarian cancer seems to persist for at least 10 years according to the CASH study (40), and most likely up to 15-20 years after stopping use (41).
The ovarian cancer risk reduction was similar for women who initiated oral contraception before 1972, when high-dose pills dominated the market; between 1972 and 1980; and after 1980, when newer, lower-dose pills dominated. Use of low-estrogen/low-progestin pills afford an estimated risk reduction (odds ratio = 0.5, 95% confidence interval: 0.3, 0.6) that is identical to that for high-estrogen/high-progestin pills (odds ratio = 0.5, 95% confidence interval: 0.3, 0.7) (42).

Endometrial Cancer And Oral Contraceptives

There is substantial evidence that OC ever-use reduces the risk of endometrial cancer by 50% (40), but the limited number of elderly women who had used OCs does not allow a definite estimate of the protection afforded after longer periods and according to duration of exposure. The reduced risk of endometrial cancer seems to persist at least 15-20 years after stopping use. In the CASH study the RR was 0.5 for 10-14 years after stopping (40); in the WHO study the odds ratio was 0.2 for high progestogen content pills more than 10 years after stopping (43). In a multicentric US study the OR was 0.3 for 15-19 years, and 0.8 for more than 20 years after stopping OC use (41). When duration and recency of use were evaluated jointly in case-control study from Washington State, longer use of OCs (>5 years) was associated with a reduced risk, irrespective of recency (44).

Cervical Cancer And Oral Contraceptives

Recent studies suggest that long duration use of OCs increases the risk of cervical cancer in HPV positive women, thus suggesting that OCs may act as a promoter for HPV-induced carcinogenesis.
In a recent systematic review the results from published studies were combined to examine the relationship between invasive and in situ cervical cancer and duration and recency of use of hormonal contraceptives, with particular attention to HPV infection. Compared with never users, the relative risk of cervical cancer increased with increasing duration of use. For duration of approximately less than 5 years, 5-9 years, and 10 or more years, respectively, the summary relative risks were 1.1 (95% CI 1.1-1.2), 1.6 (1.4-1.7), and 2.2 (1.9-2.4) for all women; and 0.9 (0.7-1.2), 1.3 (1.0-1.9), and 2.5 (1.6-3.9) for HPV positive women. The results were broadly similar for invasive and in situ cervical cancers, for squamous cell and adenocarcinoma, and in studies that adjusted for HPV status, number of sexual partners, cervical screening, smoking, or use of barrier contraceptives. The limited available data suggest that the relative risk of cervical cancer may decrease after use of OCs ceases.
Although long duration use of hormonal contraceptives is associated with an increased risk of cervical cancer, the public health implications of these findings depend largely on the extent to which the observed associations remain long after use of hormonal contraceptives has ceased, and this cannot be evaluated properly from published data (45).

Cumulative Analysis Of The Relative Risk Of Different Invasive Cancer Associated With Oral Contraceptives

Taking the 6 malignancies (breast, ovary, endometrium, uterine cervix, liver, and colon/rectum) for which there is either good or suggestive evidence of an alteration in risk associated with oral contraception, the objective of Burkman's analysis was to estimate the effect of OC use on invasive cancer in US white and black women over the age range 20 to 59 (26).
The risk of invasive breast cancer in woman age 20 to 34 is estimated to be increased by 50% (RR=1.50) among women using OCs for 4 years and by 73% (RR=1.73) among those with 8 years of OC use. The corresponding estimates of increased risk in women age 35 to 44 are 8% and 10%, respectively. For women age 45 to 59, the risk of breast cancer is estimated to be increased, non significantly, by 2% in women using OCs for 4 years, and by 3% in those with 8 years of use.
Women using OCs are at reduced risk of cancer of the ovary and endometrium. For those using oral contraception for 4 and 8 years, the risk of ovarian cancer is reduced by 40% (RR=0.60) and 51% (RR=0.49), respectively. The corresponding reductions in risk of endometrial cancer are 54% (RR=0.46) and 66% (RR=0.34), the trend being statistically significant.
Cancer of the liver and uterine cervix occur at increased rates in women using oral contraception. The risk of liver cancer is estimated to be increased 2-fold (RR=2.04) in women using OCs for 4 years and 2.6-fold (RR=2.64) in those with 8 years of use. The risk of invasive cervical cancer is estimated to be increased by 33% (RR=1.33) with 4 years of OC use and by 48% (RR=1.48) with 8

years of use, the trend being statistically significant (Table I).

Table I: Relative risk of invasive cancer associated with 4 and 8 years of OC use

	4 yrs	8 yrs	P-value
Breast			
Age 20-34	1.50	1.73	<.001
Age 35-44	1.08	1.10	.009
Age 45-59	1.02	1.03	.378
Cervix	1.33	1.48	<.001
Ovary	0.60	0.49	<.001
Endometrium	0.46	0.34	<.001
Colorectal	0.83	0.83	-
Liver	2.04	1.64	<.001

In absolute terms the estimated number of additional/fewer cases of cancer arising from age 20 to 59 per 1000 women using OCs for either 4 or 8 years depends on baseline absolute risks of different types of cancers and race considered.
In US black women 4 years of oral contraception are estimated to be associated with an additional 2.4 cases of breast cancer, 1.9 cases of cervical cancer and 0.7 cases of liver cancer. There is also an estimated reduction in risk for 3 cancer: 1.3 fewer cases of ovarian cancer, 2.4 fewer cases of endometrial cancer and 1.9 fewer cases of colorectal cancer per 1000 women. The effect is estimated to be 0.7 fewer cases of cancer by age 60 per 1000 US black women using OCs for 4 years. The corresponding net effect in US white women is estimated to be 4.2 fewer cases of cancer per 1000 women. Eight years of oral contraception is estimated to be associated with 4.0 fewer cases of cancer per 1000 white women and 0.7 additional cases per 1000 black women (Table II).
In summary, the results of this analysis suggest that the effect of oral contraception in US women is to slightly reduce their risk of invasive cancer by age 60. This is inclusive of both white and black women between the ages of 20 to 59 in the United States. Obviously, the public health impact varies by site of invasive cancer (26).

NON CONTRACEPTIVE HEALTH BENEFITS

Combined OCs bestow many benefits on users related to their contraceptive effects, including reduced risk of unintended pregnancy, less demand for abortion, decreased need for surgical sterilization, reduced maternal mortality, and less risk of other maternal or child complications.
The well-established non contraceptive health benefits of OCs are those included in the product labelling such as reduction in risk of ovarian and endometrial cancers, a decrease in menstrual disorders, decreased incidence of benign breast changes, protection against ovarian cysts and pelvic inflammatory disease (PID), and fewer ectopic pregnancies. Emerging non contraceptive health benefits include a positive effect on bone density, improvement in acne, protection against colorectal cancer, improvement in perimenopausal changes, and possible protection against rheumatoid arthritis or pelvic inflammatory disease. Thus, the benefits of these agents have expanded far beyond their ability to prevent pregnancy.

Menstrual Disorders

Primary dysmenorrhea is a significant issue for many young women during the menses. The pain of dysmenorrhea has been linked to prostaglandin release in the uterus, which is associated with increased uterine activity and responsivity to vasopressin and leukotrienes (46). Several studies have documented that OCs reduce menstrual prostaglandin release and thereby decrease uterine contractility to alleviate dysmenorrhea (46-48).
A Swedish longitudinal survey published in 1990 assessed the rate of dysmenorrhea among 596 19-year-old young women with and without low-dose OC use (47). This report noted that the prevalence and severity of dysmenorrhea was lower both at entry and after 5 years of use among those receiving any low-dose OC formulations tested (monophasic with low gestagen activity, progestogen-dominated monophasic, and triphasic) than among women who used neither a OC nor an intrauterine device (IUD) (P<.001 at 5 years of use).
OCs are commonly believed to alleviate the excessive and extended bleeding of menorrhagia. This conclusion was based predominantly on studies performed more than 30 years ago showing that high-dose OCs reduced menstrual blood loss by approximately 40% to 50% (49,50) A few more recent studies, however, have examined the effect of low-dose OCs on the extent of blood flow during the menses. In the study by Larsson 20 healthy young women with average menstrual blood loss before hormonal supplementation of 60.2±5.6 mL were entered into treatment with 30-mg EE/150-mg desogestrel. At 3 and 6 months on low-dose OCs, average blood loss had decreased to 36.5±5.2 mL and 33.7±4.1 mL, respectively (P<.001) (51). Furthermore, both the duration of menstruation and the number of women with dysmenorrhea were reduced during therapy with OCs.
Low-dose OCs also seem to be effective in treating dysfunctional uterine bleeding (DUB), including metrorrhagia, menometrorrhagia, oligomenorrhea, and/or polymenorrhea. Davis recently performed the first randomized, double-blind, placebo-controlled trial of low-dose OCs in 201 anovulatory women with DUB (52).

Table II: Added/fewer cases of cancer from age 20-59 per 1000 OC users (years of OC use)

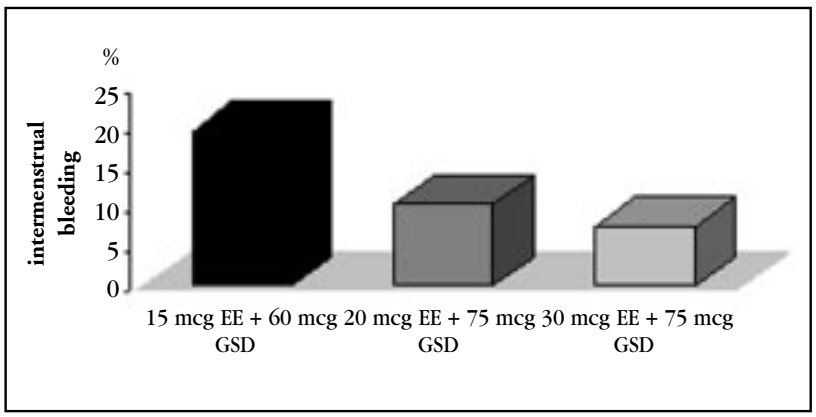
	4 yrs	4 yrs	8 yrs	8 yrs
Women	white	black	white	black
Breast	2.2	2.4	3.1	3.4
Cervix	1.4	1.9	2.1	2.8
Ovary	-2.6	-1.3	-3.3	-1.7
Endometrium	-4.3	-2.4	-5.2	-2.9
Colorectal	-1.4	-1.9	-1.4	-1.9
Liver	0.4	0.7	0.7	1.0
Total	-4.2	-0.7	-4.0	0.7

Women were randomly assigned to 3 months' treatment (3 cycles) with either placebo or a triphasic OC containing 35-mg EE/norgestimate: 0.180 mg days 1 to 7, 0.215 mg days 8 to 14, and 0.25 mg days 15 to 21. Of the evaluable subjects more than 80% of active treatment patients experienced improved bleeding patterns, based on both subject and investigator assessments compared with 36% and 45%, respectively, in the placebo group.

Functional Ovarian Cysts

Functional ovarian cysts are the result of early follicle recruitment without progression to ovulation. Thus, it is logical that hormonal manipulation with OCs, which reduces the frequency of ovulation, might also protect against the formation of these cysts. Indeed, data based on use of higher dose OCs (>50mcg EE) indicated a substantially reduced risk of functional cysts.
A series of studies in the 1970s and 1980s consistently reported fewer functional ovarian cysts among current/recent users of OCs compared with nonusers (53-56). In most cases, the incidence of cysts among past users (>6 months) was similar to that of women who had never used a OC.
Thus, it would appear that increasing ovarian suppression observed with increasing OC steroid dosages is correlated with a progressive reduction in functional cyst development. Low-dose monophasic or multiphasic pills have shown little or no effect on rates of occurrence of these cysts.

Figure 3: Incidence of intermenstrual bleeding in relation to estrogen dose



Effect On Bone Mass

Given the debilitating nature and cost of osteoporosis, ways to prevent bone loss are important. OC effects on bone are well known, and include both the established influence of estrogen (increased calcium absorption, decreased calcium loss, inhibition of osteoclasts) and the less conclusive effects of progestin (decreased urinary calcium excretion and stable or increased bone mass). Current research is focusing on using this benefit not only to control the degree of loss in bone mineral density that occurs in aging women, but in a more preventive fashion, ie, treating postmenopausal women before frank osteoporosis is diagnosed. To date, 19 studies have shown a positive effect on bone mineral density associated with OC use, and 13 studies have shown no effect; there has been no evidence of a negative effect associated with COC use in any of the studies. In 9 studies, a positive effect was noted on bone metabolism as measured by serum or urinary parameters (57). In general studies including women with altered ovarian function, as amenorrheic, or perimenopausal women, showed positive effects of Ocs on bone metabolism. A study reported by Pasco in 2000 showed that exposure to OCs was associated with a 3.3% increase in lumbar spine and vertebral BMD among premenopausal women and that BMD continued to increase modeslty with continued OC use (58).

Other Benefits of Oral Contraceptive Administration (26)

All forms of contraception should reduce the rate of ectopic pregnancy, by preventing conception, but OC have been found to have the lowest rate of all, comprising an approximate 90% reduction in risk.
OCs have been suggested to reduce PID risk via progestin-initiated thickening of the cervical mucosa and increased mucus viscosity, both of which could impede ascent of pathogens responsible for PID. Epidemiological data from earlier studies point to a substantial protective effect of OCs against acute PID. Women who used OCs have been shown to have 50%-80% lower risk of salpingitis compared with those using no contraception or a barrier method.
A excess of androgens production or peripheral action is thought to contribute to the development of acne in some patients. Because OCs reduce circulating androgen levels they have been used to treat patients with acne; progestins with low androgenic activity would be expected to be most effective in this regard.

CYCLE CONTROL WITH ORAL CONTRACEPTIVES

Combined OCs are frequently prescribed for the management of menstrual bleeding disorders such as menorrhagia and dysfunctional uterine bleeding and is highly effective for these conditions. Nevertheless, cycle control is the single most important determinant of whether a new user of the combined pill will continue the method. Although OC is the most reversible effective method of contraception, as many as half of new users stop taking OC within the first year. In fact, prominent among factors influencing discontinuation of OC is the occurrence of side effects including inter-menstrual bleeding, headache, weight gain.
Over the years the evolution of the dosage, components and phasing of OCs formulations has had an important objective: lowering total hormonal content to reduce side effects. With the decrease in doses of ethinyl-estradiol, however, there are concerns about the ability of these products to maintain a good cycle control. Bleeding disturbances during the first 3 months of use of OCs occur in up to 2% of cycles but tend to decrease with time. In a review of the literature, after 6 months of use up to 8.5% of women complain of spotting, up to 12% complain of breakthrough bleeding and 5.8% experience amenorrhoea (59). At least some of this variation is attributable to differing study populations and cultures, study designs, and the manner in which data were collected and reported.
There is also marked variation in the incidence of bleeding problems for even for the same preparation because over the years there was an evolution of the dosage, components and phasing of oral contraceptives formulations. The risk of bleeding problems certainly

depends on the dose of estrogen in combined pill and may possibly be related to the dose and type of progestins.
Comparative studies of pill formulations containing different doses of EE with the same type and dose of progestin demonstrate that there is difference in cycle control. In fact a comparative study of two OC formulations containing 150 micrograms desogestrel and either 30 micrograms or 20 micrograms EE, showed that both pills have high contraceptive reliability and are well tolerated, but with the 150/20 combination the cycle control was less effective (60).
In a comparative clinical investigation comparing two low-dose OCs containing either 20 micrograms EE/75 micrograms gestodene or 30 micrograms EE/75 micrograms gestodene, the cumulative breakthrough bleeding rates (at least once during the one year of treatment) was 14.5% for the 20 micrograms EE OC, and 11.8% for the 30 micrograms EE OC (Fig. 3). A possible management of these problems, could be prescription of the 20 micrograms EE preparation as first-line therapy in order to provide the lowest amount of EE possible. In case of persistent cycle control problems, a switch to the 30 micrograms EE drug should be considered (61). A higher incidence of intermenstrual bleeding was apparent under the 20 micrograms EE OC. A clinical investigation with a 24-day regimen containing 15 mcg ethinyl-estradiol plus 60 mcg gestodene with respect to cycle control, demonstrate that the overall incidence of intermenstrual bleeding was 19.3% (62).
The type of progestin contained in OCs can also influence the cycle control. In fact, Rosemberg's review, showed that gestodene-containing preparations appear to offer better cycle control than do desogestrel-containing preparations and levonorgestrel-containing preparations better control than norethindrone-containing preparations (59). The recent OC formulation containing 30 mcg of EE with 3 mg of drospirenone show a cycle control comparable to that experienced with other OC formulations (63).
Clinicians must alert patients to the possibility of intermenstrual bleeding and educate them with regard to the importance of continued, consistent OCs use to minimize those problems among pill users in their practice.

CONCLUSIONS

After more than 40 years from their introduction in the clinical practice, Ocs continue to be the most effective method for contraception. The progressive modifications of the doses of EE and modifications of types and doses of progestogen, has not only improved the safety of these formulations but allowed a personalization of their prescription. Overall the advantages furnished by OCs appear to outnumber the risks, and we may now confidently prescribe OCs, reassured to not arm our patients. With the advent of new formulations, new components and new route of administration available or being available in the market, our possibilities will enlarge, and likely every single patient will find the contraceptive appropriate to her need and wishes.

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